REMARKS

The present amendment is being filed with a Request for Continued Examination (RCE). Applicants understand that the amendment satisfies the requirements for submission under 37 C.F.R. § 1.114(c). Upon entry of the amendment, claims 86-98 and 100-102 will be pending, new claim 102 having been added. Support for new claim 102 can be found, *e.g.*, at page 37, lines 9-12. Claim 90 stands withdrawn as being drawn to a non-elected species. No new matter is added by the amendment.

35 U.S.C. § 103

Claims 86-89, 91-98, 100 and 101 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent No. 6,692,742 (the '742 patent) in view of Lokhorst *et al.* (*Blood* 84:2269-2277, 1994) and Masellis-Smith *et al.* (*Cancer Res.* 57:930-936, 1997).

The Examiner appears to have maintained the rejection based on the following logic. The '742 patent describes a combination of melphalen and an anti-IL-6 receptor antibody for treatment of multiple myeloma (MM). Masellis-Smith *et al.* teaches that anti-alpha4 antibodies that bind alpha4beta7 inhibited MM blood B cell interactions with bone marrow fibroblasts *in vitro*. Lokhorst *et al.* teaches that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma, and also that inhibition of this cell-cell contact inhibited IL-6 secretion by the LTBMC cells. The Examiner thus concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-IL-6 receptor antibodies taught by the '472 patent with the anti-VLA-4 antibodies taught by Masellis-Smith *et al.* or Lokhorst *et al.* in a method of treating MM. Applicants disagree for the reasons previously described and revisited below, and further in view of recent case law defining current standards of review under 35 U.S.C. § 103.

Applicants have presented evidence showing that anti-VLA-4 antibodies and anti-IL-6 receptor antibodies are not interchangeable for treatment of MM. For example, Applicants

presented evidence that anti-IL6 receptor antibodies and anti-VLA-4 antibodies will disrupt different biological pathways. In the Declaration submitted with the Reply to Office Action on September 11, 2006 ("the Mundy Declaration"), Dr. Mundy, an inventor named on the pending application, explained that an anti-IL-6 receptor antibody interacts with at least two different classes of ligands, one class being the gp130 ligands and the other class being the gp80 ligands. An anti-IL6 receptor antibody will therefore disrupt a multitude of pathways involving these ligands. See the Mundy Declaration at paragraph 7. Dr. Mundy also explained that anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6. See the Mundy Declaration at paragraph 5. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4 (as suggested by the *in vitro* findings of Lokhorst), but this would be a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells die. Applicants accordingly disagree with Examiner's conclusory statement at page 3 of the Office Action that "by inhibiting the upstream VLA-4 molecule using antibodies, the skilled in the art would be targeting the same pathway of IL-6 interaction because VLA-4 is upstream of the IL-6 production."

The Mundy Declaration also noted that the prior art reference Bataille *et al.* (*Blood* 86:685-691, 1995; cited in the IDS submitted June 21, 2002) taught that anti-IL-6 antibodies were not effective at treating MM. Bataille *et al.* reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies. See the Mundy Declaration at paragraph 4. The '472 patent also disclosed that IL-6 receptor antibodies alone were ineffective in the absence of chemotherapeutic agent. See the '472 patent at col. 20, lines 23-35; and col. 22, lines 13-20 and 49-53, and Table 2. This is in contrast to Applicants' findings, which included evidence that anti-VLA-4 antibodies alone decreased tumor burden *in vivo* in a mouse model of myeloma bone disease (see Specification at, *e.g.*, page 66, lines 14-26, and the published results in Mori *et al.* *Blood* 104:2149-2154, 2004, cited in the IDS submitted September 11, 2006). Thus, even if anti-VLA-4 antibodies inhibit IL-6 (which Examiner reads Lokhorst to suggest), one would not

expect IL-6 inhibitory agents to be interchangeable with anti-VLA-4 inhibitory agents to effectively treat MM, whether alone or in combination with any other agent.

In the Reply to Office Action submitted May 16, 2005 ("the May 16th Reply"), Applicants presented evidence of surprising results following treatment of MM with a combination therapy including anti-VLA-4 antibodies and melphalan. In the May 16th Reply, Applicants' noted the synergistic results described in the specification at page 72, lines 6-18, and Figure 8, which describes a significant decrease in serum IgG2 levels (an indicator of decreased tumor burden) in mice treated with a combination of anti-VLA-4 antibodies and melphalan. This result was surprising in view of the observation that no significant decrease was observed following treatment with either agent alone in this particular experimental model.

The U.S. Patent and Trademark Office (USPTO) now relies on KSR International Co. v. Teleflex Inc., 550 U.S. ---, 127 S.Ct. 1727 (2007), for guidance in applying the standard under 35 USC § 103. The facts in KSR concerned a small number of single references, applied in a straight-forward way to a highly predictable technology. That situation stands in stark contrast to the present matter. The present rejection relies on complicated subject matter, and three references that were applied in a complex, highly unpredictable technology. This is just the type of situation that the Supreme Court in KSR and its progeny, *e.g.*, Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 USPQ2d 1169 (Fed. Cir. 2007), cautioned against. See, *e.g.*, KSR at 1740.

In the "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*," 72 Fed. Reg. 57,526 (October 10, 2007) (hereafter, the "KSR Guidelines"), the USPTO describes rationales to support rejections under 35 U.S.C. § 103, and also states that "Office personnel should consider all rebuttal evidence that is timely presented by the applicants when reevaluating any obviousness considerations. Rebuttal evidence may include…evidence of unexpected results." KSR Guidelines at 57,534. The KSR Guidelines further state that "[o]nce the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record." KSR Guidelines at 57,535. Applicants ask that the Examiner consider all the rebuttal evidence, including the evidence of unexpected

results, in view of the entire record. Applicants maintain that the evidence as a whole indicates that one of ordinary skill in the art would not be motivated to substitute the anti-IL-6 receptor antibodies of the '472 patent with anti-VLA-4 antibodies for the treatment of MM, even in view of the disclosures of Lokhorst *et al.* and Masellis-Smith *et al.*

As stated in the Reply to Office Action mailed March 29, 2007, none of the cited references, alone or in combination, explicitly or implicitly teach or suggest treatment of MM by administering an anti-alpha4 integrin antibody, such as an anti-VLA4 antibody (or an antigen binding fragment thereof), in combination with a chemotherapeutic agent. There is also no explicit or implicit suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of the '472 patent, Masellis-Smith and Lokhorst to arrive at the claimed methods.

The Examiner states at page 5 of the Office Action that "KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness." citing Ex parte Smith, 83 U.S.P.Q.2d 1509 (B.P.A.I. 2007). However, at numerous places in KSR, the Supreme Court acknowledged that the situation is different in unpredictable arts. See, e.g., KSR at 1740 and 1741. Applicants note that the Supreme Court also stated that as long as the test is not applied as a rigid and mandatory formula, the test can provide "helpful insight" to an obviousness inquiry. KSR at 1731.

The KSR Guidelines state that "[t]he courts have made clear that the teaching, suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." KSR Guidelines at 57,534. While the Supreme Court in KSR rejected a rigid application of the teaching, suggestion, or motivation test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the art to combine" known elements in the same manner as the new invention does. KSR at 1731 (emphasis added). Such a reason does not emerge from the complex contradictory teachings in the art of from any of the statements made in the rejection. Applicants maintain that in view of the state of the art at the time the application was filed, one of ordinary skill would have found

no motivation, whether explicit or implicit, to combine the references, for at least the reasons described above.

The Supreme Court in KSR noted that

> to determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the market place; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit.

KSR at 1731 (emphasis added). Further, the key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2141(III) and MPEP 2143. In view of the state of the prior art and the knowledge of one having ordinary skill in the art at the time the application was filed, one of skill in the art would have found no reason in the '742 patent to substitute anti-IL-6 receptor antibodies with anti-VLA-4 antibodies for treatment of MM. Without an explicit reason to alter the teachings of the prior art to arrive at the presently claimed methods, the obviousness rejection fails. See KSR at 1741.

The court in Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 83 USPQ2d 1169 (Fed. Cir. 2007), applied the obviousness standard as articulated in KSR to find that claims directed to particular compounds for use as antidiabetic agents were not obvious over prior art references, at least because the references did not provide any teachings that would have led a chemist to select a disclosed compound ("compound b") for further modification to generate the claimed compounds. Significantly, while compound b was specifically claimed in a dependent claim of one prior art reference cited by the Examiner, the compound was disclosed but not identified as a preferred antidiabetic compound in a second prior art reference cited by the Examiner. Takeda at 1358. The court concluded that the teachings of the first reference were negated by the second, insofar as they applied to an obviousness analysis. Id. Similarly, while Lokhorst teaches that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to LTBMC cells *in vitro*, and inhibition of this cell-cell contact inhibited IL-6 secretion by the LTBMC cells, Applicants have presented other evidence that counters the teachings of Lokhorst at least insofar as Lokhorst may be relevant to treatments of multiple myeloma. For example,

Bataille *et al.* reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies, and the '472 patent reported that anti-IL-6 receptor antibodies alone were not effective for treatment of MM in a mouse model (see above). Thus, in view of the evidence as a whole, one of ordinary skill in the art would not have found a reason in the '742 patent to substitute the anti-IL-6 receptor antibodies of the '742 patent with an anti-VLA-4 antibody in combination with a chemotherapeutic agent for the treatment of MM, even in view of one or both of Lokhorst *et al.* and Masellis-Smith *et al.*

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

Applicants believe the claims are in condition for allowance, which action is requested.

Please apply the $810 fee for the RCE, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 10274-063001.

Respectfully submitted,

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